page 5, lines 26-34. Support for "wherein the polypeptide inhibits an interaction between AGE and cellular RAGE" may be found on page 35, lines 19-24. Accordingly, claims 1-35 are pending.

Specification

The Examiner stated that the incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication in improper. The Examiner required that applicant amend the disclosure to include material incorporated by reference. The Examiner stated that the amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins , 486 F.2d 577, 179 USPQ 167 (CCPA 193).

The Examiner stated that the attempt to incorporate subject matter into this application by reference to Schmidt et al., 1992; Neeper et al., 1992; Schmidt et al., 1994 is improper because the structure of the soluble receptor for advanced glycation end product is considered essential material. The Examiner reminded applicants that, if they wish to incorporate sequence disclosures, they have to comply with the requirements of 37 C.F.R. §1.821-1.825.

In response, applicants have amended the specification, as required by the Examiner, to include Figure 3 from Neeper et al. as Figures 4A-B in the present specification. In addition, sequence ID numbers have been assigned to the bovine and human nucleic acid and amino acid sequences (SEQ ID Nos. 1-4). Therefore, the sequence of human and bovine RAGE are no longer

incorporated by reference, but are now explicitly recited in the application. Applicants maintain that this amendment raises no issue of new matter. Applicants' undersigned attorney hereby declares that the amendment to the specification adding Figures 4A-B (Figure 3 of Neeper et al.) does not go beyond the information incorporated by reference in the present application. Support for the amendment to the specification may be found in the present specification on page 36, lines 29-32 and on page 1, lines 13-22. Neeper et al. was originally incorporated by reference and herein applicants have amended the specification to include Figure 3 of Neeper et al.

In addition, applicants will submit a Sequence Listing, floppy disk and Statement in accordance with 37 C.F.R. §1.821(f) in due course. Applicants respectfully request the Examiner to reconsider and withdraw this ground of objection.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 1-35 under 35 U.S.C. §112, first paragraph as based on a disclosure which is not enabling. The Examiner stated that the structure of the soluble receptor for advanced glycation endproduct, that is critical or essential to the practice of the invention, but not included in the claims is not enabled by the disclosure. See In re Mayhew, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The Examiner stated that this rejection might be overcome by a proper incorporation by reference as discussed above. The Examiner stated that however, issues of scope of enablement might arise concerning any/all soluble receptor for advanced glycation endproduct.

The Examiner rejected claims 1-35 because the specification does not reasonably provide enablement for "a polypeptide derived from soluble receptor for advanced glycation endproduct." The Examiner stated that the specification does not enable any person

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skilled in the art to which it pertains to make and/or use the invention commensurate in scope with these claims. The Examiner noted the discussion of derivatives (page 8, line 31 - page 9, line 8), the term "derivative" encompasses chemical modification, mutated forms, conjugates, etc. and it is unpredictable which molecule would be functional. The Examiner asserted that in view of the alleged lack of guidance and of working examples, it would constitute undue experimentation for one of skill in the art to make and/or use the invention commensurate in scope with the claims.

The Examiner asserted that the specification is not enabling "to prevent accelerated atherosclerosis in a subject predisposed thereto," or "to prevent a macrovessel disease in a subject predisposed thereto." The Examiner stated that the specification discloses examples (page 32, line 33, page 34, line 25) of treatment of diabetic mice with sRAGE, but the specification is not enabled for prevention of the diseases, because it does not provide guidance about how to determine who is predisposed to the diseases or at which stage of the disease the polypeptide should be administered. The Examiner stated that in view of the alleged lack of guidance and working examples, and as it is unpredictable who is predisposed to the disease and when the preventative treatment should be applied, it would constitute undue experimentation to make and/or use the invention commensurate in scope with the claims.

In response, applicants respectfully traverse the rejection of claims 1-35 under 35 U.S.C. §112, first paragraph. Applicants maintain that the presently pending claims are fully enabled by the specification. Applicants have amended the specification to include the sequence of human and bovine RAGE (Figure 3 of Neeper et al.) Such sequence was known to one of skill in the art at the time of filing of this application. Applicants have amended claim 1 to include reference to the structure of human

and bovine RAGE (i.e. Sequence ID Nos.: 1-4) as now explicitly shown in Figures 4A-4B. Applicants maintain that one of skill in the art at the time of filing would have known the sequence of the human and bovine RAGE polypeptide referred to in Neeper et al.

Applicants maintain that the specification fully enables "a polypeptide derived from soluble receptor for advance glycation endproduct." The amendment to the specification hereinabove has explicitly incorporated the nucleic acid sequence and the amino acid sequence of bovine and human RAGE. The specification clearly describes various ways to obtain a polypeptide derived from such sequence. The specification does not have to enable every possible embodiment of the claimed invention. However, the specification does provide a full description of conservative substitutions of sRAGE, as an example. On page 12, line 21 to page 13, line 1 the specification gives numerous examples of peptidomimetic compounds. The Examiner is further directed to page 10, line 11 to page 11, line 12 wherein a detailed description of many possible embodiments which are encompassed by the present invention are described. Applicants maintain that the specification gives a full and enabling disclosure of the presently pending claims. Applicants maintain that in view of the specification and what one of skill in the art would have known at the time of filing of the subject application, one would have a reasonable expectation of success of carrying out the presently claimed invention.

Applicants maintain that the specification fully enables one to determine who would be predisposed to accelerated atherosclerosis and macrovessel disease. Applicants respectfully direct the Examiner's attention to page 17, line 32 to page 26, line 5. Therein, the specification gives a full description of clinical signs, biochemical signs and hereditary disorders which would indicate to one of skill that a person is predisposed to

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accelerated atherosclerosis or macrovessel disease. In particular, the specification recites:

> Such clinical aspects may predispose the subject to atherosclerosis or to accelerated atherosclerosis. Thus, such subjects would benefit from the administration of a polypeptide derived from sRAGE in an effective amount over an effective time.

The specification describes various types of fatty acids and cholesterols and their locations in the body of a subject which predispose one to accelerated atherosclerosis and/or macrovessel disease. The specification states "All of these tendencies may be regarded as atherogenic." The specification further states on page 20, lines 32-35:

> Additional factors considered to play a part in coronary heart disease include high blood pressure, smoking, obesity, lack of exercise, and drinking soft as opposed to hard water.

In addition, the specification states on page 13, lines 8-11 the following:

> The subject may be suffering from an apolipoprotein deficiency. The subject may have a glucose metabolism disorder. The subject may be an obese subject. The subject may have genetically-mediated or diet-induced hyperlipidemia. AGEs form in lipid-enriched environments even in euglycemia.

Thus, applicants maintain that the specification provides a plethora of direction and information about how to determine if one is predisposed to accelerated atherosclerosis and/or macrovessel disease.

In view of the amendment to the specification and the discussion hereinabove, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

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Rejection Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 1-35 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that claim 1 is indefinite because it recites a "polypeptide derived from soluble receptor for advanced glycation product" without providing the metes and bounds of what is encompassed by "derived". The Examiner stated that such term might for example encompass mutated forms, chemical modifications, conjugates, cross-linked forms, etc.

The Examiner stated that claims 10 and 27 are indefinite because they recite "at least a portion of" and it is not clear what else should be present in the polypeptide besides a portion of the soluble receptor.

The Examiner further stated that claims 12, 13, 29 and 30 are indefinite because they do not define the structure or the metes and bounds of the polypeptide considered. The Examiner further stated that claims 13 and 30 read on any dipepetide from "the naturally occurring soluble receptor for advanced glycation product" and it is unlikely that any such dipeptide would be functional. The Examiner also stated that claim 34 lacks antecedent basis for "the sRAGE."

In response, applicants respectfully traverse the rejection of claims 1-35. Applicants have amended claims 1, 10, 13, 19, 27, 30 and 34 to more particularly point out the presently claimed invention. Applicants have amended claims 1 and 19 to clarify the metes and bounds of the polypeptide. Applicants have amended claims 10 and 27 to clarify the claimed invention. Applicants have amended claim 34 to delete "the sRAGE" and thereby rectify antecedent basis.

Applicants maintain that the presently claimed invention is fully described in the subject application and that the metes and bounds of "derived" may be found therein. The specification provides an extensive description of polypeptides derived from sRAGE. For example, the Examiner's attention is directed to the subject specification page 8, line 20 to page 12, line 1 for a description of types of polypeptides contemplated by the presently claimed invention. Clearly, such a polypeptide is preferably a competitive antagonist of the biological activity of sRAGE. See, for example, page 10, lines 11-12. The specification states on page 35, lines 21-22 "a competitive inhibitor of the interaction of AGEs with cellular RAGE." Therefore, applicants maintain that any derivative of the RAGE polypeptide which inhibits the interaction of AGEs with cellular RAGE is encompassed by the claimed invention. Many methods of derivatization are described in the specification.

Applicants have amended claims 13 and 30 to more particularly point out the presently claimed invention. Applicants disagree with the Examiner and maintain that claims 12 and 29 do clearly define the metes and bounds of the claimed invention. The phrase "wherein the polypeptide comprises a 10 kilodalton domain of naturally occurring soluble receptor for advanced glycation endproduct" clearly indicates that the polypeptide will include a 10 kilodalton domain of RAGE. Furthermore, an example of such a domain is provided in the specification, i.e. the V domain. See page 7, lines 19-24 of the specification.

In view of the amendments to the claims and the specification and the discussion hereinabove, applicants request the Examiner to reconsider and withdraw this ground of rejection.

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Rejection Under 35 U.S.C. §103

The Examiner stated that this application currently names joint inventors and in considering patentability of the claims under 35 U.S.C. §103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. The Examiner advised applicants of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. §103© and potential 35 U.S.C. §102(f) or (g) prior art under 35 U.S.C. §103(a).

The Examiner rejected claims 1-35 under 35 U.S.C. §103(a) as being unpatentable over Neeper et al. J. Biol. Chem. 267(1):14998-15004, July 25, 1992 in view of Schmidt et al., Atherosclerosis and Thrombosis 14(10): 1521-1528, and Brenton, U.S. Patent No. 5,605,885.

The Examiner stated that Neeper teach the cloning and expression of a cell surface receptor for advanced glycation endproduct (Figure 3) and defines the structural domain of the receptor (page 15000, col 2, first para.) The Examiner stated that Neeper also teach that other AGE binding proteins have been disclosed (page 15003, col 2, second full para.). The Examiner stated that Neeper do not teach a method of prevention using the soluble receptor.

The Examiner further stated that Schmidt teach a link between the accumulation of AGEs in the vessel wall and the accelerated vascular disease that occurs during the course of diabetes (page 1521, col. 2, last 5 lines). Bernton et al. teach the use of a soluble prolactin receptor to bind to and neutralize the prolactin in order to antagonize the effect of prolactin (col.

4, lines 25-40).

The Examiner stated that it would have been obvious for one of skill in the art at the time of the invention, to use a soluble receptor for AGE in order to bind with high affinity and neutralize AGEs, therefore preventing the accumulation of AGEs in the vessel wall and the accelerated vascular disease. The Examiner asserted that one would have had reasonable expectation of success in view of Bernton's teachings.

The Examiner further stated that as for the claim limitations concerning the choice of subject to be treated, the choice of fragment of the soluble receptor, the doses and methods of administration, they constitute obvious modifications for one of skill in the art.

In response, applicants respectfully traverse the rejection of claims 1-35 under 35 U.S.C. §103 over Neeper in view of Schmidt and Brenton. Applicants maintain that these references alone or in combination do not render obvious the presently claimed invention.

Neither Neeper nor Schmidt nor Bernton alone or in combination render obvious the presently claimed invention. Neeper et al. do not make obvious the presently claimed invention. Neeper merely provides the nucleic acid sequence and the amino acid sequence of human and bovine RAGE. There is no teaching of a method to prevent accelerated atherosclerosis in a subject predisposed thereto as presently claimed. Schmidt et al. do not make obvious the claimed method. Schmidt et al. merely disclose a linkage between the accumulation of AGEs and the development of diabetic complications. There is no teaching of a method for the prevention of accelerated atherosclerosis at all. There is an invitation to try or to experiment given in the last sentence of the abstract, however, there is no reasonable expectation of

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success that one of skill in the art would have been able to carry out the claimed method in view of the teaching of Schmidt and Neeper.

The teaching of Bernton does not remedy the shortcomings of Schmidt and Neeper. First, applicants maintain that there is no motivation to combine Neeper and Schmidt with Bernton. The Bernton patent is entitled "Method for Stimulating the Immune System" and Bernton discloses "methods and compositions for affecting the immune system...." (See Abstract). More particularly, Bernton discloses prolactin agonists and a vaccine adjuvant for administration to animals and humans. (See Abstract.) There would have been no suggestion or motivation for one of skill in the art to have combined Bernton with Schmidt and Neeper because Bernton discloses only compositions encompassing agonists of prolactin. Prolactin is part of the immunoglobulin superfamily and is selective for breast and pituitary tissue. Prolactin is very different from the polypeptide of the present invention. For example, prolactin receptor or growth-hormone binding receptor is found in different locations in vivo than RAGE-bearing cells and the receptors are expressed under very different physiologic conditions.

Second, soluble prolactin or growth-hormone binding receptor fragments do not make obvious the polypeptides of the presently claimed method. The clinical effect of soluble prolactin according to Bernton is to suppress the immune system. In contrast, the present invention is directed to a method to prevent accelerated atherosclerosis in a subject predisposed thereto which comprises administering to the subject a polypeptide derived from soluble receptor for advanced glycation endproduct (SEQ ID NO.: 2 or 4) in an amount effective to prevent accelerated atherosclerosis in the subject, wherein the polypeptide inhibits an interaction between AGE and cellular RAGE. Suppression of the immune system as disclosed in Bernton

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does not teach or suggest or make obvious inhibition of an interaction between AGE and cellular RAGE.

Thus, applicants maintain that Neeper in view of Schmidt in view of Bernton do not teach or make obvious the presently claimed invention. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §102(b) or 103(a)

The Examiner rejected claims 1-35 under 35 U.S.C. §102(b) or in the alternative 103(a) as obvious over Wautier et al. J. Clin. Invest. 97(1):238-243, January 1996. The Examiner stated that Wautier teaches that the soluble receptor for advanced glycation end product blocks hyperpermeability in diabetic rats (page 242, col. 1). The Examiner further stated that he teaches that increased vascular permeability is characteristic of diabetic vasculopathy, and that hyperpermeability in induced diabetic rats was largely prevented by infusion of soluble RAGE, the extracellular domain of the receptor, which blocks binding of AGEs to cell surface RAGE (page 238, col. 2, first full paragraph). The Examiner asserted that as for claim limitations concerning the choice of subject to be treated, the choice of fragment of soluble receptor, the doses and methods of administration, they constitute obvious modifications for one of skill in the art.

In response, applicants respectfully traverse the rejection of claims 1-35 under 35 U.S.C. §102(b) and §103 over Wautier et al. Although Wautier discloses sRAGE blocks hyperpermeability in diabetic rats, applicants maintain that blockage of hyperpermeability does not make obvious a method for the prevention of accelerated atherosclerosis. An increase in permeability does not specifically cause accelerated atherosclerosis, but rather indicates a broad range of possible

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vascular pathologies. Applicants point out that there is not one drug to treat hyperpermeability and therefore treat all types of vascular disease. There are various types of vascular disease which may be related to increased vascular permeability. However, Wautier et al. do not teach which diseases result from this condition, and particularly do not teach which human diseases result. Furthermore, Wautier et al. do not teach or suggest the use of a polypeptide derived from RAGE as a preventative of accelerated atherosclerosis or macrovessel disease in a subject.

Thus, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection. Applicants earnestly solicit that the Examiner allow the pending claims 1-35.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee other than the $435.00 extension of time fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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